I. Oath/Declaration

The Office Action states that the oath or declaration is allegedly defective and that a new oath or declaration in compliance with 37 C.F.R. 1.67(a) identifying this application by application number and filing date is required. The oath or declaration is defective because non-initialed and/or non-dated alterations have allegedly been made to the oath or declaration.

Applicants intend to submit a Petition to Correct Inventorship for this application. Therefore, submission of a substitute oath or declaration would not be appropriate at this time. However, once applicants have completed the necessary requirements for the Petition to Correct Inventorship, a substitute oath or declaration will be submitted to the Office at that time.

II. Rejection Under 35 U.S.C. § 112, first paragraph

The Office Action states that claims 2 and 7-10 are rejected under 35U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. According to the Office Action, the specification allegedly fails to provide an enabling disclosure for *in vivo* applications of the claimed method.

Further stated in the Office Action is that claims 1, 3-6 and 11 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for *in vitro* applications of the claimed method, allegedly does not reasonably provide enablement for *in vivo* applications of the claimed method. According to the Office Action, the claims encompass both *in vitro* and *in vivo* applications of the method. The specification allegedly fails to provide an enabling disclosure for the claimed methods because the specification teaches that the only use for the methods is for gene therapy, but the specification allegedly does not enable this use. The Office Action further states that the specification does not teach how to use the claimed methods in gene therapy applications for the following reasons.

According to the Office Action, gene therapy is not routinely successful and therefore, the disclosure must enable the full scope of the claimed methods with specific guidance. However, the specification allegedly fails to teach any method for transferring a gene into a target cell and expressing that gene at a level sufficient to produce a therapeutic effect in a diseased immunocompetent animal. The specification allegedly does not proivde any guidance as to the level of gene expression required, the number of transfected cells needed, the route and time course of administration, the site of administration, when, where, or for how long the therapeutic gene should be expressed, the frequency of administration of the gene therapy vector required, or in some embodiments, the intended target tissue, for treatment of any pathological condition in an immunocompetent animal. The specification also lacks any working examples showing that vectors of the type contemplated, once delivered to the appropriate site, would be expressed at a level sufficient to provide adequate product to effect the desired therapy in an immunocompetent animal. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. This fact is allegedly supported by various teachings available in the art at the time of filing.

The Examiner refers to an article published in Scientific American in June 1997, where Theodore Friedmann states "so far, however, no approach has definitively improved the health of a single one of the more than 2000 patients who have enrolled in gene therapy trials worldwide." The Examiner also refers to a review article published in Nature in September 1997, where Inder Verma states "although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story."

Further stated in the Office Action is that the specification fails to provide an enabling disclosure for targeting appropriate cells for *in vivo* applications of the claimed method. Only general guidance is offered with regard to targeting strategies known in the art. However, the art recognizes that targeting strategies are not currently sufficient to overcome the problems known

in the art. While progress has been made in recent years for *in vivo* gene transfer, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings in the art. The Examiner refers to Miller et al., Deonarain et al., Verma et al. and Crystal et al. in support of this statement.

The Office Action concludes that in view of the quantity of experimentation necessary to determine appropriate parameters for *in vivo* applications of the claimed method to produce a therapeutic effect in a subject, and given the lack of applicable working examples demonstrating a therapeutic effect for the claimed method, the limited guidance in the specification, the broad scope of the claims, the state of the art at the time the invention was made, the limited working example for *in vivo* gene delivery, and the unpredictability for using the claimed methods in any gene therapy application to produce a therapeutic effect, undue experimentation would have been required for one skilled in the art to practice the claimed invention.

Applicants recognize that this rejection is a "how to use" rejection under section 112. As such, the standard for showing how to use the invention is the same as the standard for showing a use (utility) in the context of section 101. Under this standard, applicants are only required to provide credible evidence that the method can be used as stated. If applicants have misconstrued the legal standard for the required showing, explicit clarification of the correct standard is respectfully requested.

Applicants respectfully point out that on pages 56-60 of the specification applicants describe *in vivo* experiments in which mice were injected either intraventricularly or intrastriatally with recombinant AAV5 β-gal (rAAV5βgal) particles, AAV2 or AAV4 particles. Applicants have provided dosages for particle delivery depending on whether injection is striatal or intraventricular. To determine which cell types in the brain were transduced by rAAV5βgal particles, representative sections of brain harvested 15 weeks after intrastriatal injection were immunofluorescently stained. Confocal microscopy was performed to assess co-localization of ß-galactosidase and representative markers. Sections were dual stained for ß-galactosidase and

either GFAP (astrocyte marker) or NeuN (neuron marker). In the striatum, many transgene-expressing cells stained positive for NeuN, indicating substantial neuronal cell transduction (see Figure 14A). After intraventricular injections, all three virions transduced primarily ependymal cells. Ependymal cell transduction was more impressive with rAAV4 and rAAV5βgal vectors.

Applicants have also shown that rAAV5βgal transduced large numbers of cells, with lasting expression in both neuronal and glial cell types (see page 58, lines 16-17). More importantly, rAAV5βgal exhibited an extensive transduction volume (see page 58, lines 17-18 of the specification). Thus, it is clear that the data provided by applicants shows that AAV5 can be utilized as a vector, *in vivo,* to target and deliver genes to specific cell types in the brain. Moreover, it is evident that upon delivery to specific cell types, expression of the gene product is extensive, sustained and in sufficient quantity.

Applicants have also provided data in the specification showing that AAV5 can be utilized as a vector to mediate gene transfer to the airways *in vivo* (page 64, line 23 to page 65, line 4). To compare the transduction efficiency of AAV5 and AAV2 *in vivo*, either AAV2 or AAV5 (1 X 10^{10} particles) was administered to 6-8 week old C57BL/6 mice. After 30 days, the mice were sacrificed, and the lungs fixed and stained with X-gal. Only minimal transduction in mice treated with AAV2/β gal was observed (see Fig. 20). In contrast, a significant increase in the number of blue cells in the lungs of mice treated with AAV5 was observed. A 15 fold increase over AAV2 transduction was observed when alveolar cells were transduced with AAV5. These data confirm that AAV5 can be utilized as a vector to transduce alveolar cells *in vivo* and is more efficient at mediating gene transfer to the luminal surface of airway epithelia than AAV2. Therefore, not only do the *in vitro* data provided in the application show increased transduction of human airway epithelia, but the *in vivo* data support the *in vitro* findings and show that AAV5 can be utilized as a vector, *in vivo,* to target and deliver genes to specific cell types in the lung. Thus, the application does provide credible evidence as to how to use the invention in a manner that enables the present claims.

In additional strong support of Applicant's enablement, subsequent to the filing date of this application, striated muscle was transduced *in vivo* according to the methods described in the present application by Chao et al. (see Exhibit A). In the present application, applicants showed that striated muscle can be effectively transduced *in vitro* by AAV5 (see Figure 8) as AAV5 transduced these cells approximately 16 fold more efficiently than AAV2. Subsequent to this finding, Chao et al. were able to efficiently transduce striated muscle *in vivo* with a recombinant AAV5 particle that expressed GFP. More importantly, Chao et al. were able to efficiently transduce striated muscle *in vivo* with a recombinant AAV5 particle that expressed canine factor IX. Canine factor IX was secreted into the plasma of experimental animals and was determined to be fully functional canine factor IX. Thus, the teachings of the present invention provide clear guidance for utilizing AAV5 as a vector for *in vivo* gene delivery. Applicants respectfully assert that the in vivo and in vitro data of the present specification, as well as the subsequent additional confirmation of applicants results, go well beyond the credible evidence required to show how to use the claimed invention.

Furthermore, the cited art relied upon by the Office, i.e. Friedmann (1997); Verma (1997); Miller et al. (1995); Deonarian et al. (1998) and Crystal et al. (1995), are all references that address the lack of success in gene therapy, prior to the present invention which provides a significant advance in adenoviral expression and targeting. It is evident, from the teachings of the specification as well as from art, that AAV5 provides significant advantages over AAV2 as an adenoviral vector, both *in vitro* and *in vivo*. Therefore, the references relied upon by the Office are inadequate to sustain an enablement rejection as the present invention overcomes a number of difficulties previously encountered in *in vivo* vector delivery. Thus, based on the *in vitro* and *in vivo* Examples provided in the specification and subsequent *in vivo* delivery of a gene utilizing recombinant AAV5 as a vector, according to the teachings of the specification, Applicant asserts that the pending claims are fully enabled and respectfully request withdrawal of this rejection.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

Payment in the amount of $920.00 is to be charged to a credit card and such payment is authorized by the signed, enclosed document entitled: Credit Card Payment Form PTO-2038. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

Gwendolyn D. Spratt

Gwendolyn D. Spratt
Registration No. 36,016

NEEDLE & ROSENBERG, P.C.
Suite 1200, The Candler Building
127 Peachtree Street, N.E.
Atlanta, Georgia 30303-1811
(404) 688-0770

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on the date shown below.

Gwendolyn D. Spratt
Gwendolyn D. Spratt

1-7-02
Date